Surgical–pathologic factors affect long-term outcomes in stage IB (pT2 N0 M0) non–small cell lung cancer: A heterogeneous disease

Chung-Ping Hsu, MD,[a,d] Jiun-Yi Hsia, MD,[a] Gee-Chen Chang, MD,[b] Cheng-Yen Chuang, MD,[a] Sen-Ei Shai, MD,[a] Shyh-Sheng Yang, MD,[a] Ming-Ching Lee, MD,[a] and Po-Cheung Kwan, MD[c]

Objectives: Our objective was to identify surgical–pathologic factors affecting prognosis in stage IB non–small cell lung cancers.

Methods: Between 1997 and 2006, a cohort of 272 cases of pT2 N0 M0 stage lung cancer were retrospectively analyzed. The patients included 70 women and 202 men with a mean age of 67.0 years. The surgical resections included pneumonectomy in 4, bilobectomy or lobectomy in 217, and limited resections in another 51. The impact of surgical–pathologic characteristics on survival, including cell type, tumor differentiation, tumor size, depth of visceral pleural invasion, type of surgical resection, and extent of lymphadenectomy on patient survival, was compared accordingly.

Results: Tumor types included adenocarcinoma/bronchioloalveolar carcinoma in 142, squamous cell carcinoma in 100, and others in 30. Cell differentiations were classified as well, moderately, and poorly differentiated in 23, 151, and 92 cases, respectively. The mean tumor size was 3.9 cm in diameter, and the average resected lymph node number was 14.3. Direct visceral pleural or subpleural invasions (<1 mm) were found in 134 and 42 cases, respectively. Angiolymphatic invasions were seen in 26 cases, and positive tumor margins were found in 14 cases. The overall 5-year and 10-year survivals were 59.5% and 41.3%, respectively. Good prognostic factors using univariate analysis included female gender, nonlimited resection, well-differentiated tumor, no angiolymphatic invasion, smaller size (≤3 cm), and numbers of nodes retrieved (>14 nodes). However, the Cox proportional hazard model revealed female gender, well-differentiated tumor, no pleural involvement, no angiolymphatic invasion, and more than 14 nodes retrieved as independent good prognostic factors.

Conclusions: Stage IB lung cancer can be treated by standard pulmonary resection accompanied by adequate mediastinal lymphadenectomy. Owing to the heterogeneity of stage IB lung cancer and the fact that prognosis can be affected by many surgical–pathologic factors, refinement of the current TNM staging criteria may be needed.

GTS

The T2 descriptors in International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) staging for NSCLCs comprise a heterogeneous group of tumors. Differences in survival of patients with stage IB (pT2 N0 M0) cancer may be caused by individualized pathologic characteristics or may be due to different T2 categories used for staging. The reported incidence of stage IB tumors was between 10% and 21%.[1,2] Surgery remains the treatment of choice for localized diseases like stage IB tumors, and the 5-year survival is between 57% and 66%.[1,2] Emphasis is on tumor size as the key denominator in prediction of outcomes of stage IB tumors.[3] The role of mediastinal lymphadenectomy in the staging and treatment of NSCLC remains controversial. Mediastinal nodal sampling is the standard in most surgical practices in North America; however, the importance of routine radical mediastinal lymph node dissection has been repeatedly raised, especially by Japanese surgeons.[2,4,5] A complete mediastinal lymphadenectomy is critical for accurate tumor staging, but its therapeutic effect is still a subject of debate.

The currently used TNM staging system for NSCLC was proposed in 1997 and has never been revised.[2] In the past decade, there has been renewed interest among chest physicians in the prognostic significance of tumor size in early-stage NSCLC. This is mainly due to the improved ability of the latest computed tomographic (CT) scanners in detecting small tumors.[6] Furthermore, a better understanding of the tumor's biological behavior has led to proposals for using tumor biomarkers as prognostic predictors.[7] In stage IB status, patients with larger tumors (>5 cm) may need adjuvant chemotherapy owing to poorer prognosis.[8] All of these findings suggest that a revision of the current staging

From the Division of Thoracic Surgery, Department of Surgery,[a] the Division of Pulmonary and Critical Care Medicine, Department of Medicine,[b] and the Department of Pathology,[c] Taichung Veterans General Hospital, Taichung, Taiwan, Republic of China; and the School of Medicine, National Yang-Ming University,[d] Taipei, Taiwan, Republic of China.

Received for publication Aug 15, 2008; revisions received Nov 27, 2008; accepted for publication Dec 24, 2008; available ahead of print March 31, 2009.

Address for reprints: Chung-Ping Hsu, MD, FCCP, Division of Thoracic Surgery, Taichung Veterans General Hospital, 160, Sec 3, Taichung-Kang Rd, Taichung 40705, Taiwan, Republic of China (E-mail: cliff@vghtc.gov.tw).

J Thorac Cardiovasc Surg 2009;138:426-33
0022-5223/$36.00

doi:10.1016/j.jtcvs.2008.12.035

Abbreviations and Acronyms

AJCC = American Joint Committee on Cancer
BAC = bronchioalveolar carcinoma
CT = computed tomography
P0 = no visceral pleural invasion
P1 = contiguous subpleural invasion
P2 = direct visceral pleural invasion
UICC = International Union Against Cancer
VPI = visceral pleural invasion (involvement)

category concerning stage IB tumors may be required. However, even the latest TNM revision for lung cancer staging proposed by the International Association for the Study of Lung Cancer ignores surgical–pathologic characteristics.[9] The aim of this study was to identify surgical–pathologic factors that affect prognosis of stage IB NSCLC based on 10 years of experience in a single institute.

PATIENTS AND METHODS

Follow-up

Between 1997 and 2006, the cases of 960 patients with primary NSCLC who underwent surgical resection in this institute were retrospectively reviewed. In this patient cohort, 323 patients with pathologic T2 N0 M0 stage among a total of 586 pT2 tumors were found. After exclusion of patients (1) who had received preoperative or postoperative chemotherapy (25 patients), (2) who had inadequate lymphadenectomy (total number of removed lymph nodes < 6) (18 patients), and (3) who had a history of additional malignancy (8 patients), a cohort of 272 patients were included in this study. The patients included 70 women and 202 men with a mean age of 67.0 years (19–87 years). During the same study period, 57 consecutive patients with pathologic T1 N0 M0 (stage IA) were also included for survival comparison. This study project was approved by the Institutional Review Board of Taichung Veterans General Hospital (No. C08126). There was no subject intervention and no identifying link to subjects.

Typically, lobectomies or pneumonectomies with systemic lymphadenectomy were performed according to institutional policy. Wedge resections or segmentectomies were performed in patients with peripheral lesions or in patients with poor performance scores or significantly impaired pulmonary function. For patients who underwent sublobar resection, lymph node sampling was performed. All pulmonary resections were performed by thoracotomy, and surgical resections included pneumonectomy in 4, bilobectomy or lobectomy in 217, and limited resections in another 51. All of the resected lymph nodes were labeled separately. The impact of pathologic characteristics on patient survival including, cell type, cell differentiation, tumor size, depth of visceral pleural invasion (VPI), type of surgical resection, and extent of lymphadenectomy, was compared accordingly. P2 indicates direct VPI, P1 indicates contiguous subpleural invasion ($\leq$1 mm), and P0 indicates no VPI. Patients with a positive resection margin were boosted with local adjuvant radiotherapy (5000–5400 rads).

Preoperative thoracic CT scan, whole body bone scanning, and liver sonography were performed on all patients to establish tumor staging and to rule out systemic metastasis. A positron emission tomographic scan was performed when mediastinal lymphadenopathy was found by CT scan. Mediastinoscopy was performed when both CT and positron emission tomographic scan showed positive mediastinal lymphadenopathy. Tumor staging and mediastinal lymph node grouping were performed according to the UICC (fifth edition) criteria.[10] Surgical–pathologic characteristics including cell type, tumor differentiation, tumor size, degree of pleural invasion, type of surgical resection, and extent of lymphadenectomy were recorded accordingly for evaluation of their impact on patient survival. The demographic data of the patients are listed in Table 1.

After discharge from the hospital, all patients were followed up at 2- to 3-month intervals until death or the end of the study period. The follow-up protocol included physical examination of patients, chest radiography, tumor markers, whole body bone scanning, liver sonography, and CT scanning of the chest every 3 to 4 months for the first 2 years and every 6 months thereafter until the fifth postoperative year.

Statistical Analysis

Cumulative survival curves were calculated and drawn by the Kaplan–Meier method and subgroups were compared by the log–rank statistic. Multivariate analyses were performed with the Cox proportional hazards model. All probabilities were 2-tailed. The statistical calculations were conducted with SPSS software (V11.0, SPSS, Inc, Chicago, Ill).

RESULTS

Current Patient Status

At the end follow-up date of this study (December 31, 2007), 164 patients were alive (including 12 patients with disease recurrence), and 108 patients were dead. Among the deceased patients, 5 (1.8%) died of postoperative complications, 19 died of other nonmalignant causes, and 84 patients died of tumor recurrence (local in 27, systemic in 35, both in 22). None of our patients were lost to follow-up during the study period. The follow-up period ranged from 12 to 129 months (mean/median, 84.1/103.6 months). To reflect the overall survival status, we did not exclude hospital mortalities and noncancer-related deaths from the survival analysis. The overall length of survival is shown in Figure 1.

Types of Resection

All pulmonary resections were performed by thoracotomy, and surgical resections include pneumonectomy in 4, bilobectomy or lobectomy in 217, wedge resection in 41, and segmentectomy in 10. The cumulative 5-year survivals for pneumonectomy, bilobectomy or lobectomy, wedge resection, and segmentectomy were 75.0%, 62.9%, 44.0%, and 40.0%, respectively, and the cumulative 10-year survivals for pneumonectomy, bilobectomy or lobectomy, wedge resection, and segmentectomy were 75.0%, 42.9%, 30.2%, and 20.0%, respectively (Figure 2, *A*; $P = .0182$). Bilobectomy or lobectomy had a better prognosis when compared with limited resection (Figure 2, *B*, $P = .0051$).

Cell Types and Tumor Differentiation

Pathologic types included adenocarcinoma in 142, squamous cell carcinoma in 100, and other types in 30. Tumors were well differentiated in 23, moderately differentiated in 151, poorly differentiated in 92, and unknown in 6. The cumulative 5-year survivals for squamous cell carcinomas, adenocarcinomas, and other cell types were 56.6%, 57.9%, and 75.4%, respectively, and the cumulative 10-year survivals were 38.0%, 40.7%, and 75.4%, respectively

TABLE 1. Demographic data on 272 patients with pT2 N0 M0 stage IB NSCLC

Variables	No. of patients
Gender	
Male	202
Female	70
Age (y)	67.0 (19–87)
Tumor location	
Right upper lobe	83
Right middle lobe	23
Right lower lobe	42
Left upper lobe	81
Left lower lobe	43
Types of resection	
Pneumonectomy	4
Bilobectomy or lobectomy)	217
Segmentectomy	10
Wedge resection	41
Extent of lymphadenectomy	
D1 (without mediastinal lymphadenectomy)	36
D2 (with mediastinal lymphadenectomy)	236
Cell types	
Adenocarcinoma	142
Squamous cell carcinoma	100
Others	30
Tumor differentiation	
Well differentiated	23
Moderately differentiated	151
Poorly differentiated	92
Unknown	6
Angiolymphatic invasion	
Yes	26
No	246
Cut margin involvement	
Yes	14
No	258
Pleural involvement	
P0 (no involvement)	96
P1 (contiguous subpleural involvement)	42
P2 (direct pleural involvement)	134

NSCLC, Non–small cell lung cancer.

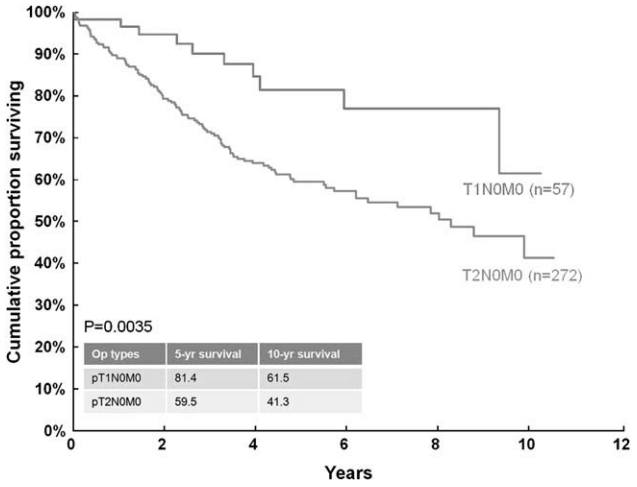

FIGURE 1. Overall survival times of 57 patients with pT1 N0 M0 (stage IA) and 272 patients with pT2 N0 M0 (stage IB) non–small cell lung cancer after resection.

(Figure 3, *A; P* = .1506). In the adenocarcinoma group, 9 were pure bronchioalveolar carcinoma (BAC), and 23 had a focal BAC pattern. The cumulative 5-year survivals for pure adenocarcinoma, adenocarcinoma with focal BAC, and pure BAC were 54.3%, 67.6%, and 74.2%, respectively, and the cumulative 10-year survivals in pure adenocarcinoma, adenocarcinoma with focal BAC, and pure BAC were 35.8%, 67.6%, and 49.4%, respectively (*P* = .2056). Pure BAC and BAC-containing adenocarcinoma showed a trend toward better prognosis when compared with pure adenocarcinoma (Figure 3, *B; P* = .0763). In regard to tumor differentiation, well-differentiated tumors had the best survival (84.4% at 5 years and 67.5% at 10 years) as compared with their counterparts (Figure 4; *P* = .0008).

Tumor Size

The tumor size ranged between 1 and 13 cm in diameter (mean 3.9 cm). Thirty-six (13.2%) tumors were 2 cm or less in diameter, and 107 (39.3%) tumors were 3 cm or less in across. Patients with tumors 2 cm or less in diameter had a better prognosis than their counterparts (*P* = .0493); patients with tumors 3 cm or less in diameter also had better prognosis than their counterparts (Figure 5; *P* = .0159). Subgroup analysis of patients with tumors 3 cm or less in diameter who also had pleural involvement (P2) did not demonstrate survival differences when compared with their counterparts (*P* = .1327). Similar findings were observed when the cutoff size was changed to 2 cm or less in diameter (*P* = .2126).

Visceral Pleural Involvement (VPI)

Direct visceral pleural (P2), subpleural invasion (P1), and no pleural invasion were found, respectively, in 134, 42, and 96 cases. The cumulative 5-year survivals for the P0, P1, and P2 groups were 64.3%, 58.7%, and 56.1%, respectively, and the cumulative 10-year survivals in the P0, P1, and P2 groups were 41.1%, 50.3%, and 36.6%, respectively (Figure 6, *A; P* = .3393). Intergroup comparisons (P0 vs P1, P1 vs P2, P0 vs P2, P0 vs P1+P2, P0+P1 vs P2) did not show significant differences in survivals. Tumors without pleural involvement (P0) were smaller than their counterparts (3.71 ± 1.22 cm vs 4.06 ± 2.03 cm; *P* = .073). Subgroup analysis of patients with P2 lesions who also had tumors 3 cm or less in diameter did not demonstrate survival differences when compared with their counterparts (*P* = .1694). Similar findings were observed when the cutoff size was changed to 2 cm or less in diameter (*P* = .2705). However, when P2 and P1 lesions were combined, tumors of 3 cm or less (2.52 ± 0.56 cm) demonstrated better survivals than did their counterparts (5.16 ± 1.98 cm) (Figure 6, *B; P* = .0153).

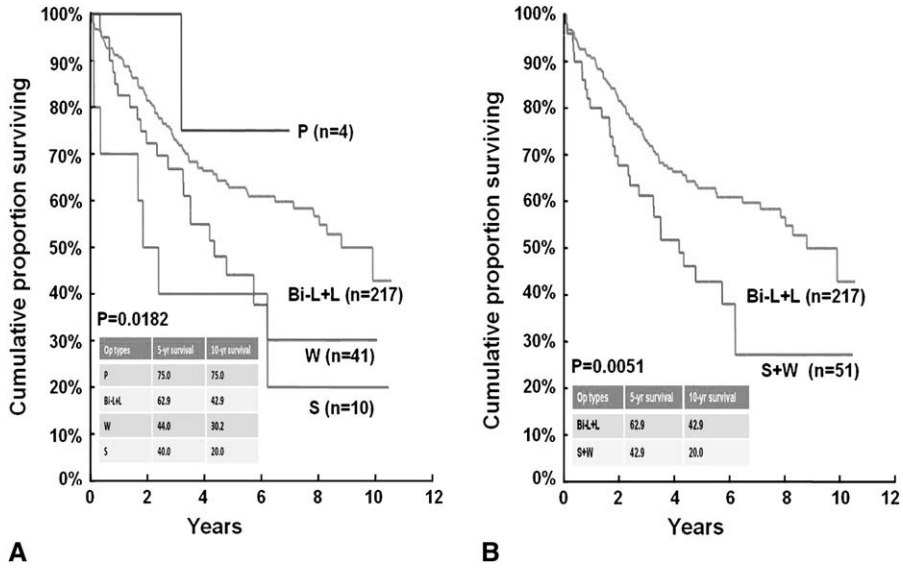

FIGURE 2. Survival analysis according to the types of resection. A, Survival curves for *P* (pneumonectomy), *L* (lobectomy), *Bi-L* (bilobectomy or lobectomy), *W* (wedge resection), and *S* (segmentectomy). B, Survival curves according to standard resections and limited resections.

Extent of Nodal Dissection

The total number of retrieved nodes was between 6 and 58 (mean 14.3). The average numbers of retrieved nodes in N1 and N2 stations were 5.4 and 8.9, respectively. Patients with more than 14 retrieved nodes had 5-year and 10-year survivals of 71.1% and 53.8%, respectively (Figure 7, *A;* $P = .0049$). The majority of patients (86.8%) had received at least one mediastinal nodal station lymphadenectomy (D2 dissection in 236; 1 to 5 stations, mean, 2.2 stations). Patients who received D2 dissection had better outcomes than did patients who received D1 dissection (without mediastinal lymphadenectomy) (Figure 7, *B;* $P = .0019$).

Angiolymphatic Invasion and Resection Margin

Angiolymphatic invasions were identified in 26 (9.6%) tumors, and patients with these tumors had a poorer prognosis (29.6% at 5 years and 29.6% at 10 years) than did their counterparts (62.7% at 5 years and 43.1% at 10 years; Figure 8; $P = .0068$). Positive resection margins were found in 14 (5.1%) patients, including 9 at the bronchial cut end

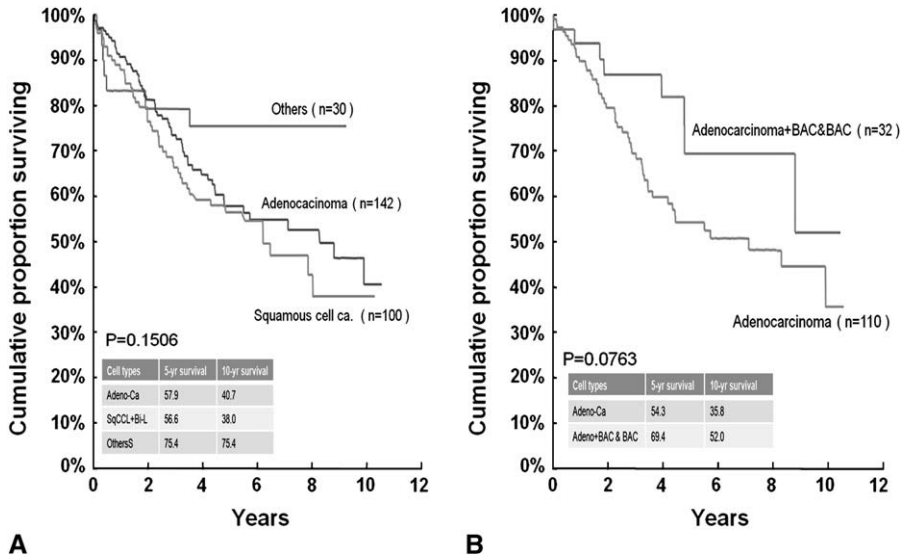

FIGURE 3. Survival analysis according to tumor types. A, Survival curves for squamous cell carcinomas, adenocarcinomas, and other cell types. B, Survival curves according to the presence of BAC (bronchioloalveolar carcinoma) patterns. *Adenocarcinoma+BAC,* Adenocarcinoma with focal BAC component; *BAC,* pure bronchioloalveolar carcinoma.

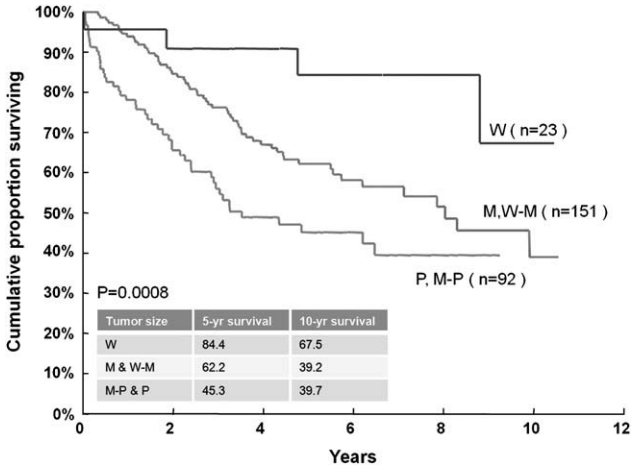

FIGURE 4. Survival analysis according to cell differentiation. Well-differentiated *(W)* tumors had 5-year and 10-year survivals of 84.4% and 67.5%, respectively. *M,* Moderately differentiated; *P,* poorly differentiated.

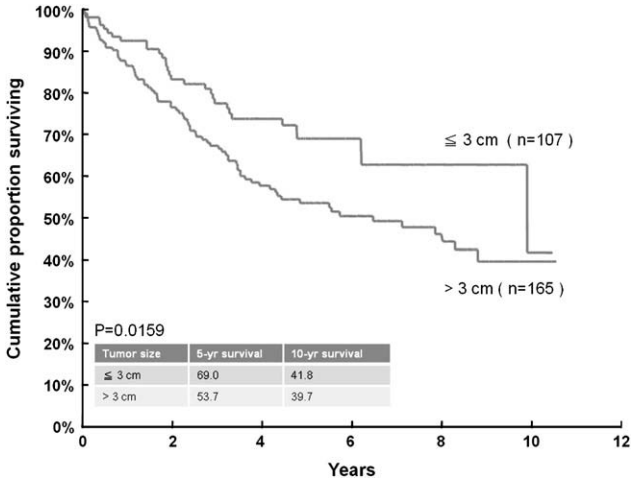

FIGURE 5. Survival analysis according to tumor size. Patients with tumors less than 2 cm and 3 cm in diameter both had better long-term survivals than did their counterparts.

and 5 at the peribronchial soft tissue. No survival differences were found between the two groups ($P = .3548$).

Cox Proportional Hazards Survival Analyses

Important prognostic factors such as gender, operation type, pathologic cell type, tumor differentiation, tumor size, pleural involvement, angiolymphatic invasion, and extent of lymphadenectomy were incorporated into the Cox proportional hazards model. Independent prognostic indicators included gender ($P = .0008$), tumor differentiation ($P = .0024$), pleural involvement ($P = .0130$), angiolymphatic invasion ($P = .0500$), and number of lymph nodes retrieved ($P = .0118$). The hazard ratio and 95% confidence interval for individual parameters are listed in Table 2.

DISCUSSION

Although sublobar resection is thought to be associated with increased incidence of local recurrence when compared with lobectomy, El-Sherif and associates[11] found no difference in disease-free survival between the two types of resection in patients with stage IA disease, but slightly worse disease-free survival for those with stage IB. Kraev and colleagues[12] reported patients with tumors less than 3 cm in size had improved survival times after lobectomy. In the current study, only 4 (1.5%) patients required pneumonectomy owing to central location or proximity to vessels. The majority of patients had lobectomy or bilobectomy (79.8%). When compared with sublobar resection, survival benefits were observed (62.9% vs 42.9% at 5 years; $P = .0051$). Lobectomy is a time-honored procedure for stage IB tumors.

Tumor size plays a critical role in determination of prognosis, especially in early-stage lung cancers without nodal metastasis. Data from the Surveillance, Epidemiology, and End Results registry demonstrated that when tumors were small (<2 cm), lung cancer–associated mortality was similar for adenocarcinoma and squamous cell carcinoma. In tumors 3 cm or larger in size, lung cancer–associated mortality was higher for adenocarcinoma.[13] Mizuno and coworkers[14] reported that stage IB cases with BAC-dominant histologic characteristics had lower rates of lymphatic permeation, vascular invasion, and pleural invasion. The distribution of adenocarcinomas and squamous cell carcinomas was similar in our series; moreover, long-term survivals of the two groups were similar, too (Figure 3, *A*). We[15] previously reported a better surgical outcome in patients with localized (nodular) type BAC tumors compared with diffuse (infiltrative) type. Pure BAC and focal BAC patterns were found in 22.5% (32/142) of the adenocarcinomas in the current study. Subgroup comparison survival between pure adenocarcinomas and BAC-containing adenocarcinomas showed a trend toward better outcomes in the latter group (Figure 3, *B*). In regard to tumor differentiation, moderately and poorly differentiated tumors comprised more than 90% of the whole series. Although less frequently encountered, well-differentiated tumors showed the best survival (84.4% at 5 years and 67.5% at 10 years), which is almost the same as that for stage IA tumors (Figure 4).

Asamura and coworkers,[16] using the Japanese Lung Cancer Registry data, suggested T1 tumors could be divided into T1a (≤2.0 cm at the greatest diameter) and T1b (2.1–3.0 cm at the greatest diameter) subcategories according to size. In the proposed staging system, the authors defined T1a N0 M0 as new stage IA and T1b N0 M0 as new stage IB. T2 N0 M0 (stage IB) and T1 N1 M0 (stage IIA) were combined and defined as new stage IIA.[16] Our data indicated that patients with tumors 3 cm or less in diameter survived better than their counterparts. If we change the cutoff diameter to 2 cm, the survival difference between the two groups persists ($P = .0493$).

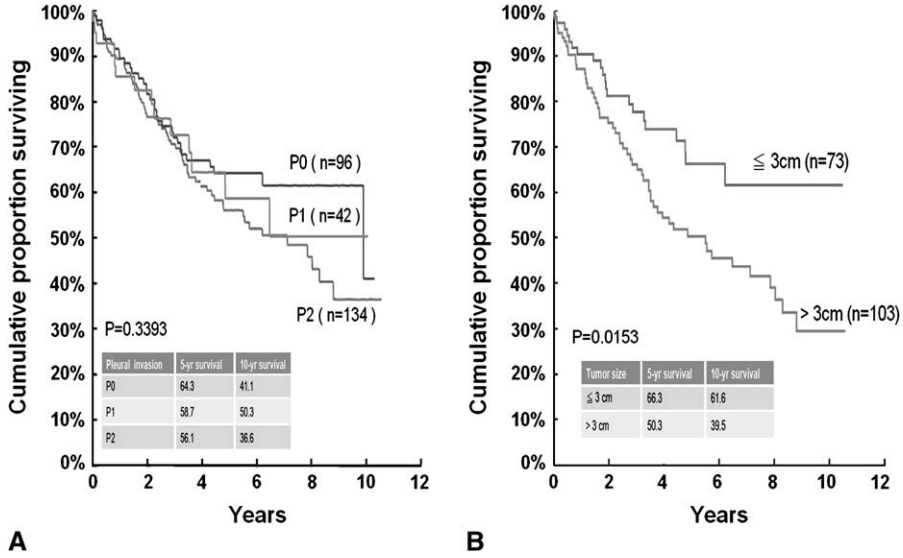

FIGURE 6. A, Survival analysis according to the depth of visceral invasion in all groups. B, After exclusion of P0 group, patients with tumors of 3 cm or less in diameter had better long-term survivals than did their counterparts.

There is a paucity of literature on the prognostic significant of VPI and the number of patients with stage IB NSCLC in whom staging is done solely according to VPI. In tumors less than 3 cm in diameter, the distinction between stages IA and IB depends on existence of VPI. Disruption of elastic lamina, the key histologic landmark, is essential for diagnosis of VPI.[17] Taube and coworkers[18] suggested that routine elastic tissue staining should be performed as a standard method for assessing pleural involvement in pleura-based NSCLC owing to false negatives for VPI that occurred in 19% of the group stained with hematoxylin and eosin alone. In the current study, we divided the tumors into P0, P1, and P2 subgroups according to the depth of VPI. Using a similar classification, Ohta and colleagues[19] reported patients with P2 showed a significantly poorer survival and shorter disease-free interval than did patients with P0 and P1. Our patient cohort demonstrated an actual 5-year survival of 64.3% in the P0 group. Intergroup comparison failed to demonstrate significant survival differences (Figure 4). However, Cox proportional hazards model revealed VPI as an independent prognostic factor ($P = .0131$).

Mizuno and associates[14] identified tumors without pleural invasion as a subgroup with a better outcome in stage IB adenocarcinoma. The 5-year survival of those 76 patients was almost the same as that of patients with stage IA adenocarcinoma. On the other hand, the 5-year survival for patients with

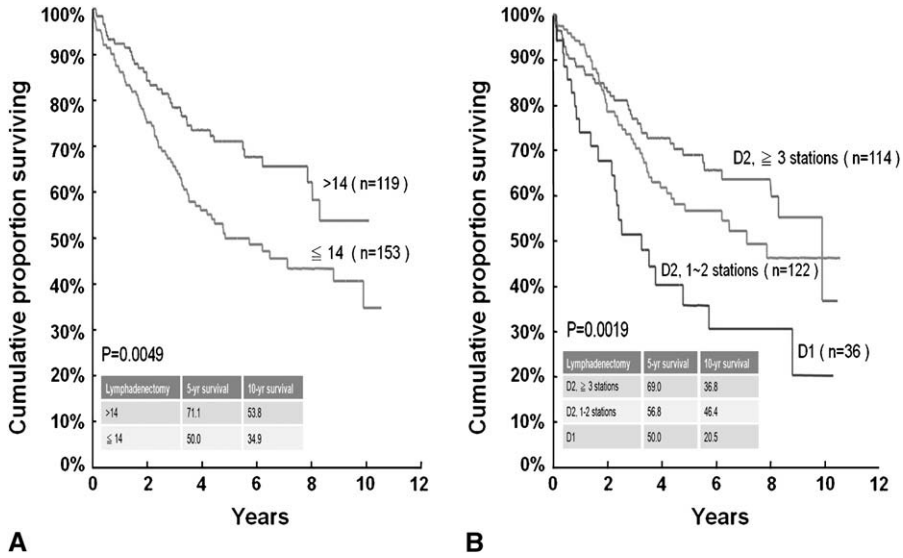

FIGURE 7. Survival analysis according to the extent of lymphadenectomy. Patients who received a more extensive lymphadenectomy (A, retrieved nodes >14; B, D2 dissection) also had a better outcome.

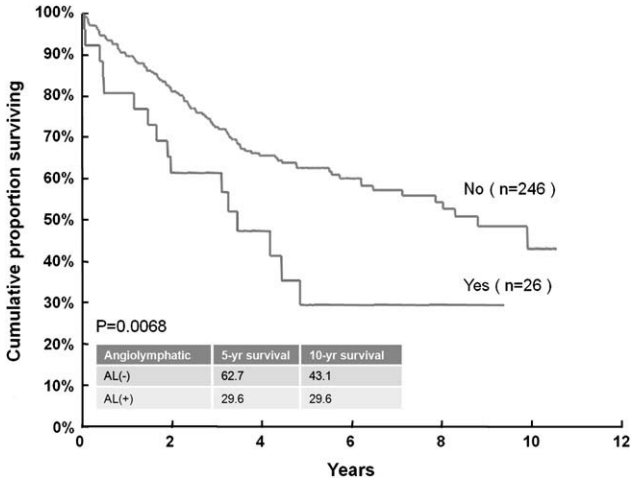

FIGURE 8. Survival analysis according to the presence of angiolymphatic *(AL)* invasion. Patients who had tumors with positive microscopic angiolymphatic invasion had a poorer prognosis.

stage IB disease with pleural invasion was significantly poorer than that for patients with stage IB disease without pleural invasion. These data suggest that visceral involvement itself is a poor prognostic factor. Nevertheless, a report based on data from the California Cancer Registry indicated 43.2% of the stage IB tumors were staged owing to VPI (T2P).[3] The authors claimed that small T2P tumors (≤3 cm) were a favorable prognostic factor with survival similar to that for patients with stage IA disease. Their data indicate that VPI carries an increased mortality risk, but this mortality risk is dependent on the size of the tumor. These findings have also been confirmed by Hung and associates,[20] demonstrating that small tumors (<3 cm) of stage IB (T2 N0 M0) NSCLC with VPI should be treated as T1 disease and not T2 disease owing to better outcomes. Consistent with the report by Ou and associates,[3] our study showed that tumors with VPI (P2+P1) were indicative of a significant decline in survival once the tumor size was larger than 3 cm (Figure 6, *B*). In brief, our data indicated that impact of VPI on survival is closely related to the tumor size.

By avoiding stage migration, complete mediastinal lymphadenectomy provides the best possibility for accurate tumor staging and survival benefits.[4,21-23] The main purpose of this study was not to address specifically the extent of lymphadenectomy. However, we found significant survival benefits after extensive lymphadenectomy (>14 nodes, Figure 7, *A*). Moreover, when 3 or more mediastinal nodal stations were removed in the lymphadenectomy, patients survived longer than their counterparts (Figure 7, *B*). Recently, prospective studies have demonstrated that selective mediastinal dissection for clinical–surgical stage I NSCLC is as effective as complete dissection.[24,25] This is very important in the era of minimally invasive thoracoscopic surgery on small tumors. If complete mediastinal lymphadenectomy is unnecessary in early-stage NSCLC, then morbidities related to mediastinal dissection can be avoided and operation time can be shortened. A recent large series report conducted in the United States covering a 15-year study period also demonstrated a tendency toward more extensive lymphadenectomy.[26] The authors concluded that a higher number of lymph nodes removed was associated with statistically significant improvements in overall survival and lung cancer–specific survival of patients with stage IA NSCLC who underwent lobectomy. In the Cox proportional regression analysis, they found that removal of 11 to 15 lymph nodes conferred the lowest hazard ratio for mortality. These findings were consistent with our experiences.

Blood vessel and lymphatic vessel invasions, especially in small tumors, have been identified as important prognostic factors.[2,14,27] Tsuchiya and associates[28] showed that prognosis of patients who have stage IA disease with vessel invasion is similar to that of patients with stage IB NSCLC and

TABLE 2. Multivariate survival analysis by the Cox proportional hazards model of 272 patients with pT2 N0 M0 stage IB NSCLC

Risk factors	Coefficients (SE)	Relative risk (95% CI)	*P* value*
Gender			.0008
Female (n = 67)		1	
Male (n = 195)	0.99 (0.29)	2.69 (1.51–4.79)	
Types of resection			.4468
Bi-L+L (212)		1	
S+W (n = 51)	0.2 (0.27)	1.23 (0.72–2.08)	
No. of LN retrieved			.0118
>14 (n = 116)		1	
≤14 (n = 146)	0.59 (0.23)	1.80 (1.14–2.84)	
Extent of lymphadenectomy			.1060
D2 (n = 228)		1	
D1 (n = 34)	0.47 (0.29)	1.60 (0.90–2.84)	
Cell types			.4027
SqCC (n = 96)		1	
Adeno-Ca (n = 142)	0.19 (0.23)	1.21 (0.77–1.91)	
Others (n = 24)	–0.33 (0.42)	0.72 (0.32–1.63)	
Differentiation			.0024
WD (n = 23)		1	
MD (n = 148)	1.33 (0.53)	3.79 (1.33–10.76)	
PD (n = 91)	1.78 (0.55)	5.91 (2.01–17.37)	
Tumor size			.2478
≤3 cm (n = 101)		1	
>3 cm (n = 161)	0.26 (0.23)	1.30 (0.83–2.03)	
Pleural involvement			.0131
P0 (n = 91)		1	
P1+P2 (n = 171)	0.56 (0.23)	1.75 (1.12–2.72)	
Angiolymphatic invasion			.0500
No (n = 237)		1	
Yes (n = 25)	0.55 (0.28)	1.73 (1.00–2.98)	

NSCLC, Non–small cell lung cancer; *SE,* standard error; *CI,* confidence interval; *Bi-L+L,* bilobectomy and lobectomy; *S+W,* segmentectomy and wedge resection; *LN,* lymph nodes; *D2,* with mediastinal lymphadenectomy; *D1,* without mediastinal lymphadenectomy; *SqCC,* squamous cell carcinoma; *Adeno-Ca,* adenocarcinoma; *WD,* well differentiated; *MD,* moderately differentiated; *PD,* poorly differentiated; *P0,* no pleural invasion; *P1+P2,* contiguous subpleural and direct pleural invasion. **P* value by Wald statistic.

can be enhanced by postoperative oral uracil–tegafur chemotherapy to improve long-term survival. Nearly 10% of our patients had a pathologically proven tumor island within the lumen of a small vessel or lymphatic channel of the tumor. The clinical significance was reflected by the overall survivals, which were as low as 29.6% at 5 years. Fourteen (5.1%) patients with microscopic positive cut margins did not show decreased survival ($P = .3548$), which may be due to small patient numbers or a good response to postoperative local radiotherapy.

Taken together, the above results demonstrated that the accuracy of the T category in predicting prognosis according to the current TNM staging system is limited by its focus on the size and location of the tumors regardless of the tumor's biomolecular behaviors. Consistent with the report of Jones and colleagues,[29] we found factors causing 5-year survivals of less than 60% included a cell type of pure adenocarcinoma, a larger tumor size (>3 cm), existence of direct and contiguous subpleural invasion, existence of angiolymphatic invasion, a limited pulmonary resection, and a less extensive mediastinal lymphadenectomy. Among these, the pathologic findings in particular may indicate the need to up-stage the tumor as stage IIA. In another way, the current TNM staging system may need to be annotated using stage IB(+) to indicate a more promising (favorable) outcome or stage IB(–) to indicate a more negative (unfavorable) outcome for patients with the same stage IB disease.

In summary, stage IB NSCLC comprises a heterogeneous group of node-negative tumors with different prognoses. The current staging system includes tumors either with a prognosis similar to that of stage IA tumors or with a prognosis the same as that of stage IIA tumors. This discrepancy may cause confusion in decisions about postresectional adjuvant therapy. Modification of the current TNM staging criteria by up-staging or annotation and taking consideration of the surgical–pathologic factors that cause 5-year survivals of less than 60% may be needed to make the forthcoming version of UICC/AJCC TNM staging manual one that more accurately reflects recent findings.

We thank Ms H. C. Ho (Biostatistics Task Force of Taichung Veterans General Hospital, Taichung, Taiwan, Republic of China), Ms J. Miao, and Ms S. Y. Wang for their assistance in data collection and statistical analysis.

References

1. Mountain CF. Revision in the International System for staging lung cancer. *Chest*. 1997;111:1710-7.
2. Asamura H, Goya T, Yoshimura H, Koshiishi Y, Sohara Y, Eguchi K, et al. A Japanese Lung Cancer Registry Study: prognosis of 13,010 resected lung cancers. *J Thorac Oncol*. 2008;3:46-52.
3. Ou SH, Zell JA, Ziogas A, Anton-Culver H. Prognostic significance of the non-size-based AJCC T2 descriptors: visceral pleura invasion, hilar atelectasis, or obstructive pneumonitis in stage IB non-small cell lung cancer is dependent on tumor size. *Chest*. 2008;133:662-9.
4. Naruke T. Significance of lymph node metastases in lung cancer. *Semin Thorac Cardiovasc Surg*. 1993;5:210-8.
5. Sugi K, Nawata K, Fujita N, Ueda K, Tanaka T, Matsuoka, et al. Systematic lymph node dissection for clinically diagnosed peripheral non–small cell lung cancer less than 2 cm in diameter. *World J Surg*. 1998;22:290-5.
6. Henschke CI, Yankelevitz DF, Smith JP, Miettinen OS. Small stage I cancers of the lung: genuineness and curability. *Lung Cancer*. 2003;39:327-30.
7. Brundage MD, Davies D, Mckillop WJ. Prognostic factors in non–small cell lung cancer. A decade of progress. *Chest*. 2002;122:1037-57.
8. Christian C, Erica S, Uliano M. The prognostic impact of tumor size in resected stage I non–small cell lung cancer: evidence for a two thresholds tumor diameters classification. *Lung Cancer*. 2006;54:185-91.
9. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta P, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol*. 2007;2:706-14.
10. International Union Against Cancer. Lung tumours. In: Sobin LH, Wittekind CH, eds. TNM classification of malignant tumours. 5th ed. New York: Wiley-Liss; 1997:91-7.
11. El-Sherif A, Gooding WE, Santos R, Pettiford B, Ferson PF, Fernando HC, et al. Outcomes of sublobar resection versus lobectomy for stage I non–small cell lung cancer: a 13-year analysis. *Ann Thorac Surg*. 2006;82:408-16.
12. Kraev A, Rassias D, Vetto J, Torosoff M, Ravichandran P, Clement C, et al. Wedge resection vs. lobectomy: 10-year survival in stage I primary lung cancer. *Chest*. 2007;131:136-40.
13. Ost D, Goldberg J, Rolnitzky L, Rom WN. Survival after surgery in stage IA and IB non–small cell lung cancer. *Am J Respir Crit Care Med*. 2008;177:516-23.
14. Mizuno T, Ishii G, Nagai K, Yoshida J, Nishimura M, Mochizuki T. Identification of a low risk subgroup of stage IB lung adenocarcinoma patients. *Lung Cancer*. 2008 (doi:10.1016/j.lungcan.2008.03.032 in press).
15. Hsu CP, Chen CY, Hsu NY. Bronchioloalveolar carcinoma. *J Thorac Cardiovasc Surg*. 1995;10:374-81.
16. Asamura H, Goya T, Koshiishi Y, Sohara Y, Tsuchiya R, Miyaoka E. How should the TNM staging system for lung cancer be revised? a simulation based on the Japanese Lung Cancer Registry populations. *J Thorac Cardiovasc Surg*. 2006;132:316-9.
17. Hammar SP. Common neoplasms. In: Dahl DH, Hammar SP, eds. Pulmonary pathology. New York: Springer-Verlag; 1994:1123-78.
18. Taube JM, Askin FB, Brock MV, Westra W. Impact of elastic staining on the staging of peripheral lung cancers. *Am J Surg Pathol*. 2007;31:953-6.
19. Ohta Y, Waseda R, Minato H, Endo N, Shimizu Y, Matsumoto I, et al. Surgical results in T2N0M0 nonsmall cell lung cancer patients with large tumors 5 cm or greater in diameter: what regulates outcome? *Ann Thorac Surg*. 2006;82:1180-4.
20. Hung JJ, Wang CY, Huang MH, Huang BS, Hsu WH, Wu YC. Prognostic factors in resected stage I non–small cell lung cancer with a diameter of 3 cm or less: visceral pleural invasion did not influence overall and disease-free survival. *J Thorac Cardiovasc Surg*. 2007;134:638-43.
21. Izbicki JR, Passlick B, Pantel K, Pichimeier U, Hosch SB, Karg O, et al. Effectiveness of radical systematic mediastinal lymphadenectomy in patients with resectable nonsmall cell lung cancer: results of a prospective randomized trial. *Ann Surg*. 1998;227:138-44.
22. Gajra A, Newman N, Gamble GP, Kohman LJ, Graziano SL. Effect of number of lymph nodes sampled on outcome in patients with stage I non–small cell lung cancer. *J Clin Oncol*. 2003;21:1029-34.
23. Wu YC, Lin C-FJ, Hsu WH, Huang BS, Huang MH, Wang LS. Long-term results of pathological stage I non–small cell lung cancer: validation of using the number of totally removed lymph nodes as a staging control. *Eur J Cardiothorac Surg*. 2003;24:994-1001.
24. Yoshimasu T, Miyoshi S, Oura S, Hirai I, Kokawa Y, Okamura Y. Limited mediastinal lymph node dissection for non–small cell lung cancer according to intraoperative histologic examinations. *J Thorac Cardiovasc Surg*. 2005;130:433-7.
25. Okada M, Sakamoto T, Yuki T, Mimura T, Miyoshi K, Tsubota N. Selective mediastinal lymphadenectomy for clinico–surgical stage I non–small cell lung cancer. *Ann Thorac Surg*. 2006;81:1028-32.
26. Ou SH, Zell JA. Prognostic significance of the number of lymph nodes removed at lobectomy in stage IA non–small cell lung cancer. *J Thorac Oncol*. 2008;3:880-6.
27. Bréchot JM, Chevret S, Charpentier MC, Vecchi CA, Capron F, Prudent J, et al. Blood vessel and lymphatic vessel invasion in resected nonsmall cell lung carcinoma. *Cancer*. 1996;78:2111-8.
28. Tsuchiya T, Akaminea S, Muraoka M, Kamohara R, Tsuji K, Urabeb S, et al. Stage IA non–small cell lung cancer: vessel invasion is a poor prognostic factor and a new target of adjuvant chemotherapy. *Lung Cancer*. 2007;56:341-8.
29. Jones DR, Daniel TR, Denlinger CE, Rundall BK, Smolkin ME, Wick MR. Stage IB nonsmall cell lung cancers: are they all the same? *Ann Thorac Surg*. 2006;81:1958-62.